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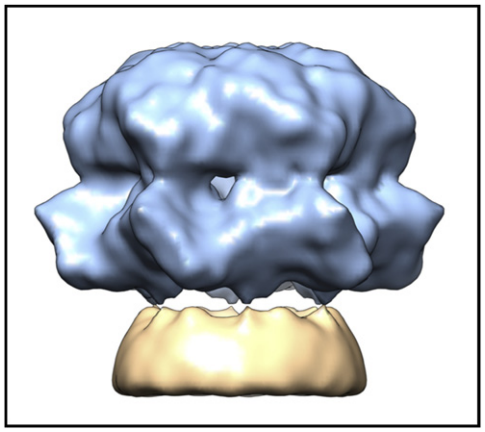
In This Issue

Local and Global Mobility in the ClpA AAA+ Chaperone



PAGE 553

Cells must be able to digest designated cytoplasmic proteins in order to advance through the cell cycle and to eliminate defective or toxic proteins. Such activity must be stringently controlled to protect bona fide components and is handled by combining a complex that recognizes targets with a degradative complex. Cryoelectron microscopy of the ClpAP complex of *E. coli* by Effantin et al. now provides a detailed account of a fully assembled degradation machine. It turns out to be highly mobile, whereby transitions in different parts of the complex cooperate to unfold substrate proteins and feed them into the degradation chamber. (Figure dapted from Effantin et al.)

Amyloidogenicity Hangs on a Single Mutation

PAGE 563

Peterson et al. previously reported that amyloidogenic light-chain protein AL-09 dimerizes in an abnormal manner compared to the germline protein (κI O18/O8), suggesting that the dimer interface plays a role in amyloid formation. Here, using NMR, the authors solve structures of two related mutants. AL-09 H87Y adopts the normal dimer, but κI Y87H presents an abnormal dimer rotated 180° relative to the normal dimer and 90° from the AL-09 arrangement. The results suggest that dynamic rearrangements in the light-chain dimer interface are the first steps in the amyloid formation, providing valuable information for future rational drug design strategies for this devastating disease.

Apoptosome-Procaspase-9 CARD Complex

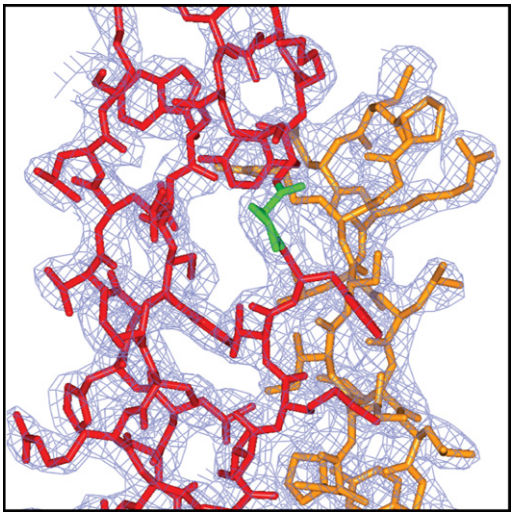
PAGE 571

Human Apaf-1 coassembles with cytochrome c to form the 7-fold symmetric apoptosome. This complex then binds and activates a protease, known as procaspase-9 (pc-9). Yuan at al. determined a 3D structure of an apoptosome-procaspase-9 CARD complex at ~9.5 Å resolution and modeled the wheel-like platform. The central hub is constructed like other AAA+ protein rings but also contains novel features. Remarkably, Apaf-1 CARDs are disordered in the ground state. However, during pc-9 activation, each Apaf-1 CARD interacts with a pc-9 CARD to form a flexibly-tethered "disk" that sits above the central hub. Together, the data reveal conformational changes that occur during Apaf-1 assembly to allow pc-9 activation.

Prp19 WD40 Domain Uses the Blades

PAGE 584

Prp19 is a member of the WD40-repeat family of E3 ubiquitin ligases and a conserved eukaryotic RNA splicing factor essential for activation and stabilization of the spliceosome. To understand the role of the WD40 repeat domain of Prp19 Van der Kooi et al. have determined its structure and functional interactions. They find that the domain adopts a distorted seven bladed WD40 architecture with a highly conserved surface that is required for the physical interaction between Prp19 and Cwc2 and yeast viability. Further, two molecules of Cwc2 bind to the Prp19 tetramer, providing a model for the functional architecture of Prp19 in the spliceosome. (Figure adapted from Van der Kooi et al.)



HYPONASTIC LEAVES1 with miRNA Touch

PAGE 594

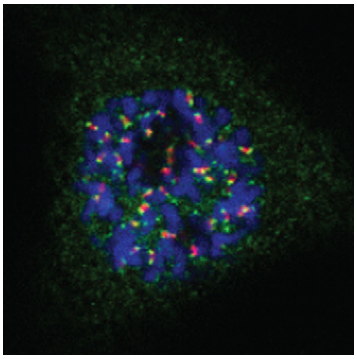
The *Arabidopsis* HYPONASTIC LEAVES1 (HYL1) is a double-stranded RNA-binding protein that plays a significant role in facilitating miRNA processing. In this work, Yang et al. report crystal structures of HYL1 dsRBD domains that, together with biochemical and genetic analysis, provides molecular insights into the miRNA processing mechanism, including the dimerization property of HYL1 and the putative mode of action of HYL1 binding to miRNA/miRNA* region.

Mycobacterium tuberculosis PknB Extracellular PASTA

PAGE 606

PknB is a transmembrane Ser/Thr protein kinase from *Mycobacterium tuberculosis*, and a PknB homolog from *Bacillus subtilis* was proposed to be a receptor for a signaling molecule that promotes the exit of dormancy after binding to the extracellular domain known as PASTA domain. In *M. tuberculosis*, the exit of dormancy, called resuscitation, is a mechanism of a particular importance as it leads to the outbreak of the disease. Barthe et al. now report an NMR structure of the entire external domain of PknB. The four PASTA modules display an unexpected linear organization, suggesting a ligand-dependant activation mechanism for PknB.

RZZ Complex Related to Multisubunit Vesicle Tethering Machinery



PAGE 616

The ZW10 protein works in the spindle checkpoint to promote accurate chromosome segregation. ZW10 is also implicated in retrograde vesicular trafficking. Çivril et al. demonstrate that ZW10 is part of two structurally related complexes, the RZZ and the NRZ, and provide detailed structural information on ZWILCH, an RZZ subunit. They also show that ROD and NAG, respectively subunits of the RZZ and NRZ, consist of a β-propeller and an α-solenoid. This organization is typical of clathrin, COP-I, and nucleoporins. Thus, the RZZ, which is limited to metazoans, might have evolved from evolutionary conserved complexes implicated in vesicular trafficking and nuclear transport. (Figure adapted from Çivril et al.)

Regulatory Nascent Chain and the Ribosome

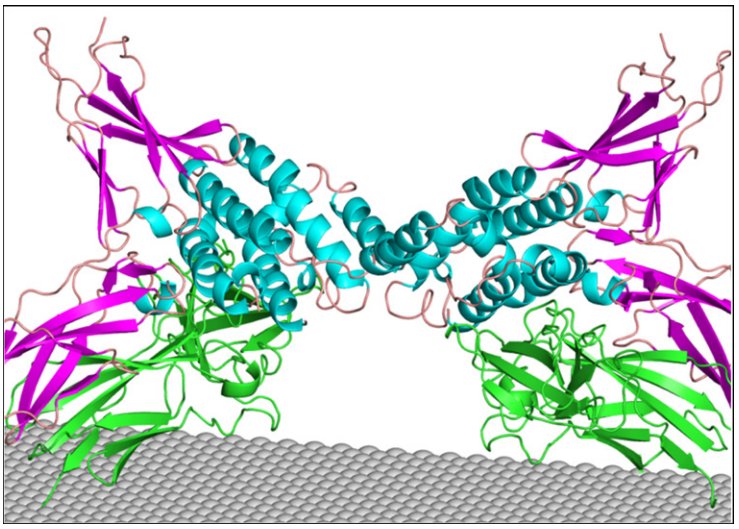
PAGE 627

Regulatory nascent chains interact with the ribosomal exit tunnel and modulate their own translation. A classical example is TnaC, the leader peptide of the tryptophanase operon. By combining cryoelectron microscopy data with a range of computational techniques, Trabuco et al. characterized how the ribosome recognizes critical TnaC residues at the atomic level. Specifically, TnaC residue Trp12 is recognized via a cation-pi interaction by Arg92 of ribosomal protein L22, whereas TnaC residue Asp16 forms salt bridges with ribosomal proteins, in particular with Lys90 of L22. The results also suggest nascent chain elements that may prevent translational arrest in various organisms.

IL-10R2 Common Chain: Not So Tight!

PAGE 638

A common problem in cell and structural biology is characterizing weak protein-protein interactions. In this report, Yoon et al describe a crystal structure of the IL-10R2 chain. IL-10R2 chain is known to bind five different cytokines with low affinity. Interfaces between IL-10R2 and three different cytokines (human IL-10, cmvIL-10, and IL-22) were mapped by alanine scanning, and the data was used to derive computer-based docking models of the activated cytokine receptor complexes. These low-affinity interfaces, while structurally quite similar, exhibit partially distinct energetic epitopes. This data may be used to predict the function of IL-10R2 single nucleotide polymorphisms (SNPs) found in inflammatory bowel disease. (Figure adapted from Yoon et al.)



CD44 Adhesiveness in Equilibrium

PAGE 649

This study by Ogino et al. reveals a key structural feature underlying the cell rolling mediated by CD44, a principal hyaluronan receptor involved in lymphocyte homing and tumor metastasis. The authors demonstrate that the hyaluronan-binding domain (HABD) of CD44 exists in an equilibrium between low- and high-affinity conformations, in both the presence or absence of the ligand. Moreover, using a mutant that only adopts the high-affinity conformation, the two-state equilibrium was shown to be critical for the CD44-mediated cell rolling. The results provided an intimate linkage between the dynamic property of the adhesion molecule at the structure level and the adhesiveness of leukocyte at the cellular level.

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